Cholinesterase activity in serum during general anesthesia in health and disease

Yitzhak Brzezinski Sinai
Tel Aviv Sourasky Medical Center
Ester Zwang
Tel Aviv Sourasky Medical Center
Elena Plotnikova
Tel Aviv Sourasky Medical Center
Esti Halizov
Tel Aviv Sourasky Medical Center
Itzhak Shapira
Tel Aviv Sourasky Medical Center
David Zeltser
Tel Aviv Sourasky Medical Center
Ori Rogowski
Tel Aviv Sourasky Medical Center
Shlomo Berliner
Tel Aviv Sourasky Medical Center
Idit Matot
Tel Aviv Sourasky Medical Center
Shani Shenhar-Tsarfaty (shanis@tlvmc.gov.il)
Tel Aviv Sourasky Medical Center

Research Article

Keywords: Cholinesterase, Acetylcholinesterase, General Anesthesia

Posted Date: January 9th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-137940/v1

Version of Record: A version of this preprint was published at Scientific Reports on August 17th, 2021. See the published version at https://doi.org/10.1038/s41598-021-96251-5.

Abstract

Atherosclerotic patients challenge the anesthesiologist as they display a significant instability between the two parts of the autonomic nervous system. We aimed to assess the effect of general anesthesia (GA) and surgery on serum cholinesterase activity.

Prospective study of 57 patients undergoing ambulatory or vascular surgery under GA. Cholinesterase levels were measured before induction of anesthesia, 15 minutes thereafter and at the end of surgery by measuring the capacity of serum Acetylcholinesterase (AChE) and Butyrylcholinesterase to hydrolyze AcetylThioCholine. Data of atherosclerotic disease, anesthesia management were analyzed.

Both AChE and total Cholinergic Status (CS) decreased significantly after GA induction at 15 minutes and furthermore by the end of surgery. Vascular surgery patients, presented lower baseline cholinesterase activity compared to patients for ambulatory surgery. In patients requiring intraoperative administration of phenylephrine for hemodynamic support (21.1%), a significant lower level of AChE and CS was observed compared to untreated patients. A positive correlation was found between the lowest temperatures measured and the AChE and CS change from the baseline values. Our findings serve as a mirror to the sympathetic/parasympathetic disbalance during GA with a marked decrease in the parasympathetic tone. Our data show that low cholinesterase activity increase the need for hemodynamic support.

Introduction:

General anesthesia influences blood flow to body organs,[1] in part through anesthetics direct effect on central and peripheral nervous systems.[2] that result in vasodilation / vasoconstriction and alteration in cardiac function.[3] During general anesthesia, the autonomic nervous system (ANS) function is assessed by indirect measurements such as blood pressure, heart rate, body temperature, and plethysmography.[4] Controlling ANS – induced hemodynamic shifts, that result in part from anesthetic drugs, is one of the most critical tasks of the anesthesiologist.[5] In addition, patients who suffer from atherosclerosis, and specifically from coronary atherosclerosis, may further challenge the anesthesiologist as they might display a significant instability between the two parts of the ANS (sympathetic and parasympathetic).[6,7]

Cholinergic status is determined by the equilibrium of production and degradation of acetylcholine (ACh). The process of degradation in the central and peripheral ANS is done by acetylcholinesterase (AChE) and Butyrylcholinesterase (BChE).[8] Although acetylcholine is the natural substrate of AChE, one previous study suggests that BChE influences ACh degradation more than AChE perhaps due to its higher quantity in the plasma.[9] Yet, the physiologic role of BChE is not clear, but the common hypothesis is that this enzyme has a protective effect against different toxins.[10]

Recently, a correlation was found between activity levels of AChE and BChE to resting heart rate, systolic and diastolic blood pressure, cholesterol, body mass index (BMI), metabolic syndrome characteristics and

heart rate recovery in healthy adults.[6,11–14] Repetitive measurements of BChE activity levels during 5 years show little variation in healthy adults.[15] In contrast, following acute events, such as myocardial infarction or stroke, decreased level of both cholinesterase were observed which were associated with worse prognosis.[16]

Data regarding anesthesia and surgery effects on cholinesterase activity levels are limited. During general anesthesia, the anesthesiologist uses different drugs that inhibit competitively the activity of cholinesterase, for example neostigmine.[10,17–20,21]Also, a recent study found that cholinesterase activity could be related to post-operative delirium.[22] In the present study we aimed to assess the effect of general anesthesia and surgery on cholinesterase activity levels [10,23] and to evaluate whether patients with atherosclerotic disease demonstrate altered activity levels when compared to healthy adults. Additionally, we aimed to examine in patients undergoing general anesthesia whether there is an association between enzyme activity levels and hemodynamic stability.

Materials And Methods:

Study population

This is a comparative prospective study. The study was approved by the Tel Aviv Sourasky Medical Center ethics committee, conformed to the principles outlined in the declaration of Helsinki (0342-19-TLV), and informed consent was obtained from all participants.

Two groups of patients undergoing surgery under general anesthesia of longer than one hour were enrolled. The first group of patients have known atherosclerotic disease (coronary, peripheral vascular or cerebral) arriving for vascular surgery. The second group are patients for ambulatory surgery without known atherosclerotic disease. Patients were enrolled consecutively from November 1st, 2019 to December 30th 2019.

Inclusion criteria –men and women, age > 18, who can sign informed consent, with either known atherosclerotic disease or no such background, scheduled for either a planned vascular surgery or ambulatory surgery, respectively. The surgery is assumed to last more than an hour of anesthesia time.

Exclusion criteria patients with medical history of Parkinson or Alzheimer disease, known muscle paralysis diseases with characteristics of muscle nerve synapse injury, acute kidney injury by KDIGO criteria.[24]

Cholinesterase activities

Blood samples were taken from all patients at three time points; prior to, and 15 minutes after induction of anesthesia, and at the end of surgery prior to neuro-muscular blockade reversal agent administration (Neostigmine).

We used the ACh analog Acetylthiocholine (ATCh) as a substrate that is hydrolyzed by both ACh degrading enzymes (Acetylcholinesterase and Butyrylcholinestersase) and reflects the total serum capacity for acetylcholine hydrolysis, referred to as Cholinergic Status (CS). (appendix 1)

Serum samples were frozen at − 80 °C until acetylcholine hydrolysis analysis. Acetylcholinesterase and total cholinesterase activity levels were assayed in triplicates in a microtiter plate using an adaptation of the Ellman assay.[25] Hydrolysis of 1 mM acetylthiocholine (ATCh, Sigma) was followed by spectrofluorometry (Spectrafluor Plus, Tecan) at 405 nm.(appendix 2) Prior to read, we incubated the samples for 20 min in the dark with (for acetylcholinesterase activity) or without (for total cholinesterase activity) 50 μM tetra isopropyl pyrophosphoramide (iso-OMPA, Sigma) which is a specific ButyrylCholinestersase inhibitor. We calculated enzyme activity using 13,600 M/cm as the e405 for 5-thio-2-nitrobenzoate.[26,27]

Intra-operative measurements

Data of anesthesia management were taken from the Metavision with the aid of MDclone novel program: medications given during anesthesia including hypnotic, analgesics, sympathomimetics (Ephedrine, Phenylephrine) and Norepinephrine, type of anesthesia (total intravenous anesthesia versus volatile anesthesia), lowest temperature measured during anesthesia.

Primary outcome- to characterize the dynamics of cholinesterase activity in patients undergoing general anesthesia and surgery.

Secondary outcome- to assess the association between cholinesterase activity and hemodynamic instability during general anesthesia reflected by the intraoperative use of vasopressors.

Statistical analysis

All continuous variables are displayed as means (SD) for normally distributed variables or median [interquartile range] for variables with abnormal distribution. Categorical variables are displayed as numbers (%) of subjects within each group.

To test differences in continuous variables between 2 groups, the independent-samples t-test or the Mann–Whitney test were performed. For comparison of dichotomous or categorical variables, the Pearson Chi-Square test was performed. To compare continuous variables between 2 time-points the paired-samples t-test was performed or the sign-rank test when needed. The Pearson or Spearman correlation coefficients were used to assess correlations between continues variables. To compare continuous variables between 3 time points the repeated-measures general linear model was used. A one-way Analysis of Variance (ANOVA) with a linear contrast was used to compare the CS values between vascular and non-vascular groups for blood pressure measurements and In order to identify possible confounders, a multivariate regression with the use of pressor drugs (sympathomimetics and Norepinephrine) was used controlling for the age, and department as covariates. $P < 0.05$ was considered

statistically significant for all-analyses. We used IBM SPSS Statistics 24 statistical package (IBM Corporation, Armonk, New York, USA) for all statistical analysis.

Results:

Patient's demographics

During the study period 57 patients were enrolled, of whom 17 (29.8%) underwent vascular surgery (peripheral arterial bypass surgery or carotid endarterectomy) and 40 (70.2%) underwent ambulatory surgery, mainly lumpectomy or laparoscopic cholecystectomy. Their demographics are presented in Table 1. Third of the cohort suffered from essential hypertension, almost all treated with angiotensin receptor blocker/ angiotensin converting enzyme inhibitor (ACEI/ARB) while some with more than one medication (beta blockers or calcium channel blockers). Anemia [28] was found in 9 patients (15.7%). Comorbidities associated with atherosclerotic disease such as myocardial infraction, carotid artery stenosis, peripheral vascular disease, cerebrovascular disease affected 14%, 7%, 17.5%, 3.5% of patients, respectively, and were prevalent only in the vascular surgery group. Comorbidities and patients' medications are listed in Table 1.

Table 1
Demographics, Comorbidities & medications

Table 1	**Population demographics, Comorbidities & medications**
Table 2	Cholinesterase activity at baseline, 15 minutes after induction of anesthesia and at the end of anesthesia
Table 3	Drug and anesthesia methods and their effect on Cholinesterase activity at baseline, 15 minutes after induction of anesthesia and at the end of anesthesia
Figure 1 (a,b)	Mean AChE activity (a) and total cholinergic status (b) in vascular vs. non-vascular patients by time of measurement during anesthesia (baseline, 15 minutes and at the end of surgery)
Figure 2 (a,b)	Correlation between minimal body temperature and the delta of AChE (a) and total cholinergic status (b) from the baseline to the end of anesthesia
Patients characteristics	
Age, years, mean(SD)	52.3 (19.1)
Gender, % male, n (%)	23 (40.4)
Body mass index- BMI, kg/m^2, mean(SD)	25.5 (5.0)
Smoking, n (%)	25 (43.9)
Surgical and Post Anesthesia Care Unit details	
Department, n (%):	
Vascular	17 (29.8)
General surgery	26 (45.6)
Nose Ear Throat	7 (12.2)
Urology	1(1.75)
Plastic	6 (10.5)
American Society of Anesthesiologists-ASA Physical Status Classification System, n (%):	
1	12 (21.1)
2	28 (49.1)

Others: Congestive heart failure, Cerebrovascular disease, Chronic obstructive pulmonary disease, Hematologic tumor, Obstructive sleep apnea

Table 1	Population demographics, Comorbidities & medications
3	14 (24.6)
4	3 (5.3)
Anesthesia length, min, median (IQR)	85.0 (47.5–124.0)
Post Anesthesia Care Unit length of stay, min, median (IQR)	195.0 (100.5-327.5)
Parameter	n (%)
Essential hypertension	18 (31.6)
Myocardial infraction	8 (14)
Anemia	9 (15.7)
Carotid artery stenosis	4 (7)
Peripheral vascular disease	10 (17.5)
Diabetes Mellitus	7 (12.3)
Chronic kidney disease	4 (7)
Tumor	14 (24.5)
Depression	5 (8.8)
Beta blockers	7 (12.3)
Calcium channel blocker	8 (14)
Angiotensin receptor blocker/ Angiotensin converting enzyme inhibitor	15 (26.3)
Others	11 (19.5)
Others: Congestive heart failure, Cerebrovascular disease, Chronic obstructive pulmonary disease, Hematologic tumor, Obstructive sleep apnea	

Cholinergic enzyme activity and status

Primary outcome:

Both AChE and total cholinergic status (CS) decreased significantly after general anesthesia induction at 15 minutes and furthermore by the end of surgery (Table 2).

Table 2
Cholinesterase activity at baseline, 15 minutes after induction of anesthesia and at the end of anesthesia

	Baseline	15 min after induction of anesthesia	Paired p-value	End of anesthesia	Paired p-value(compared to baseline)	Paired p-value (compared to 15 min)
AChE, nmol/min/ml	453.7 ± 216.8	403.4 ± 201.1	**< 0.001**	384.8 ± 201.5	**< 0.001**	**0.029**
Cholinergic Status, nmol/min/ml	1396.2 ± 614.8	1241.1 ± 568.0	**< 0.001**	1165.8 ± 568.9	**< 0.001**	**0.005**
AChE- measurement achieved after incubating the samples with tetra isopropyl pyrophosphoramide a specific ButyrylCholinestersase inhibitor. Followed by spectrofluorometry using ACh analog acetylthiocholine (ATCh) as a substrate for the enzyme.						
Cholinergic Status CS- spectrofluorometry using ACh analog acetylthiocholine (ATCh) as a substrate for the enzyme, without incubating with tetra isopropyl pyrophosphoramide.						

The mean delta decrease in enzymatic activity, using paired format from baseline to 15 min post induction of anesthesia was 70.5 ± 91 $p < 0.001$; 234.7 ± 278.2 $p < 0.001$, for AChE and CS respectively, and from baseline to end of anesthesia the mean delta was 50.3 ± 76.9 $p < 0.001$; 155.1 ± 191.7 $p < 0.001$, respectively. This finding remained significant after repeated measurement for linear regression adjusted for age, gender, BMI, department and ASA Physical Status Classification System.

When comparing the two main groups (vascular surgery patients vs. ambulatory surgery in patients without atherosclerotic disease) a significant difference of cholinesterase activity was present already at baseline with lower levels for the vascular surgery patients (327.9 ± 101.9 vs. 506.8 ± 228.6 for AChE; 1035.7 ± 343.7 vs. 1551.5 ± 635.1 for CS, respectively $p < 0.001$ for both). During general anesthesia significant decreases in both AChE and CS from baseline measurement to 15 minutes after induction of anesthesia were observed only in the ambulatory surgery group (patients without atherosclerotic disease), with further significant reduction by the end of anesthesia compared to baseline measurement (Fig. 1a, 1b).

Secondary outcome

Vasopressor support and cholinesterase activities

The association between vasopressors use (reflecting the need to optimize hemodynamics) and cholinesterase activity before and following anesthesia was assessed. In patients requiring intraoperative administration of phenylephrine for hemodynamic support (n = 12, 21.1%), a significant lower levels of AChE and CS was observed at the beginning and at the end of anesthesia compared to patients not treated with phenylephrine ($p = 0.008$ and $p = 0.013$ for AChE; $p = 0.011$ and $p = 0.011$ respectively, Table

3). No differences in enzyme levels was found when comparing patients who received ephedrine (n = 19, 33.3%) vs. those who did not at any of the time points measured.

Table 3
The effect of drug and anesthesia methods on Cholinesterase activities

Drug		Baseline	Paired p-value	15 min after induction of anesthesia	Paired p-value	End of anesthesia	Paired p-value
Phenylephrine (n = 12, 21.1%)	AChE[a]	364.5 + 71.9	**0.008**	340 + 94.72	0.067	300.6 + 87.8	**0.013**
	AChE[b]	477.1 + 233.9		420.64 + 219.07		407.7 + 217.8	
	CS[a]	1152.5 + 223.3	**0.011**	1035.42 + 184.33	**0.019**	935.8 + 222.5	**0.011**
	CS[b]	1463.0 + 662.8		1297.25 + 623.69		1232.5 + 612.5	
Ephedrine (n = 19, 33%)	AChE[a]	431.1 + 119.4	0.496	375.5 + 138.4	0.529	332.7 + 174.6	0.167
	AChE[b]	464.7 + 250.2		417.7 + 227.1		411.6 + 211.3	
	CS[a]	1322.9 + 354.2	0.427	1182.1 + 412.1	0.393	1006.8 + 477.9	0.124
	CS[b]	1435.1 + 704.7		1271.5 + 636.6		1252.2 + 592.6	
Remifentanil)n = 11, 19.3% (	AChE[a]	360.1 + 115.8	0.109	313.1 + 94.5	**0.013**	305.8 + 96.2	**0.029**
	AChE[b]	475.8 + 227.7		425.4 + 214.4		404.1 + 216.1	
	CS[a]	1118.3 + 377.5	0.091	1000.9 + 315.7	**0.030**	934.4 + 310.6	**0.031**
	CS[b]	1464.5 + 637.8		1299.8 + 602.2		1226.2 + 599.0	
Type of anesthesia (n = 8, 14%)	AChE[c]	578.25 + 260.03	0.076	503.9 + 269.2	0.128	479.6 + 257.0	0.152
	AChE[d]	433.1 + 202.47		386.6 + 185.7		369.0 + 189.4	
	CS[c]	1798.88 + 792.35	**0.044**	1561.5 + 726.8	0.085	1411.7 + 691.2	0.191

AChE- Acetylcholinesterase; CS- Cholinergic Status, both measured in nmol/min/ml;

[a]- treated, [b]- not treated, [c]- TIVA- Total intravenous anesthesia, [d]- Volatile anesthesia,

Drug		Baseline	Paired p-value	15 min after induction of anesthesia	Paired p-value	End of anesthesia	Paired p-value
	CS[d]	1332.16 + 557.17		1187.7 + 527.7		1128.4 + 538.2	
AChE- Acetylcholinesterase; CS- Cholinergic Status, both measured in nmol/min/ml;							
[a]- treated, [b]- not treated, [c]- TIVA- Total intravenous anesthesia, [d]- Volatile anesthesia,							

Other outcome

Temperature

A positive correlation was found between the lowest temperature measured during anesthesia and the AChE and CS change from the baseline values (r = 0.309, for both, p = 0.039). (Fig. 2)

This correlation remains significant even following adjustment for anesthesia length (r = 0.324, p = 0.034; r = 0.322 p = 0.035 for AChE and CS respectively)

Remifentanil infusion

Remifentanil is an ultrashort opioid which metabolized by non-specific blood and tissue esterase, but its effect on cholinesterase activity has not been studied to date. We found that patients receiving remifentanil continues infusion (n = 11, 19.3%) presented similar baseline measurements when compared to patients that did not receive remifentanil, but significant decrease of AChE and total CS 15 minutes after induction of anesthesia was observed (p = 0.013; p = 0.03, respectively) which remain significant also at the end of anesthesia (p = 0.029; p = 0.031, respectively, Table 3). The results remained significant even after adjustment for vasopressors use.

Type of anesthesia and cholinesterase activities

To further investigate the reason for decline of AChE and CS activity during general anesthesia we compared patients who were under total intra venous anesthesia (TIVA) (n = 8, 14%) vs. patients receiving volatile anesthesia (VA). We found that patients under TIVA had higher levels of CS at the baseline measurement compared to VA group (p = 0.044). All other comparisons of cholinesterase activities between TIVA to VA did not reach significance levels.

Discussion:

Knowledge regarding the effect of general anesthesia and surgery on cholinesterase activity levels is scarce. This is the first study to show a decrease in cholinesterase activities during general anesthesia; significant decrease in AChE and total Cholinergic Status (CS) levels were found at 15 minutes post general anesthesia induction and at the end of surgery compared to baseline levels. Additionally, the

present study demonstrated that vascular patients admitting for elective surgery show significantly lower levels of AChE and CS at baselined and during anesthesia when compared to non-vascular patients. The results might have clinical implications. Previous study by Arbel et al. found that patients arriving for cardiac catheterization with lower levels of cholinesterase had higher risk for major adverse cardiac events.[29] Goliash et al. report that low cholinesterase could be used as a biomarker for mortality prediction in stable coronary artery disease.[30]

In the present study, lower levels of cholinesterase activities during surgery and anesthesia were associated with higher demand for drugs that support hemodynamics such as phenylephrine or ephedrine. As our department follows good clinical practice[31] of keeping mean arterial pressure 65 mmHg or more, this association is a reflection of the prevalence of hypotension with the anesthesiologists actively treating hypotension to prevent postoperative morbidities. To the best of our knowledge, this is also the first time that direct plasma measurements of cholinergic activity were assessed in order to reflect peripheral sympathetic/parasympathetic balance during anesthesia. Current review of the anesthesia literature suggests the use of heart rate variability tracking as a surrogate marker for sympathetic response and for the analgesics management in clinical practice. [32,33] Our method offers a more precise measurement for evaluating the cholinergic tone, in addition to the HRV measurement.

Anesthetics and cholinesterase during anesthesia

Holtkamp et al. suggested a possible link between propofol, a hypnotic drug, and decrease in cholinesterase activity through the effect propofol had on expression and methylation of cholinergic genes.[34] The methodology involved immersion of cells in very high concentration (25mcg/ml) of propofol for very long period of time (2–4 hours), not resembling the pharmacokinetics in the human body and the clinical concentrations used in anesthesia. Our data did not find difference between patients undergoing anesthesia using total intravenous anesthesia with propofol and patients anesthetized using volatile anesthetics suggesting that the type of agent used for general anesthesia did not explain the decrease in cholinesterase activity level we found.

Remifentanil, a synthetic ultrashort opioid analgesic has ester linkage which undergoes hydrolysis by non-specific plasma esterase,[35] In vitro studies showed that remifentanil is not a good substrate for plasma cholinesterase.[10] Nevertheless we found significant lower levels of cholinesterase for patients that were anesthetized using remifentanil. A possible explanation is the known decreased sympathetic tone when using remifentanil which might extrapolate higher parasympathetic tone. Further studies will be needed to investigate on this finding.

Body temperature and Cholinesterase during anesthesia

We found a correlation between lowest body temperature measured during anesthesia to the level of AChE and CS. Furthermore, the decline in cholinesterase levels was correlated with lower body temperature. This finding is in line with the need for higher vasopressor use and the low level seen in the

vascular group. Another possible explanation is low enzymatic activity in cold in-vivo environment, however, the lab measurement was done under temperature control.

Our study has few limitations; first, this is a relatively small group size, thus further studies are needed in larger patient population, more so when assessing sub-populations. Second limitation is that baseline enzyme activity measurement was done at the entrance to the operating room when we might assume that the patient is anxious thus it might not reflect the true baseline of the patient, but rather anxious state before surgery.[36,37] However, this measurement was done in the same setting for all patients.

In summary, the main finding of our study is that anesthesia and surgery induced a significant reduction in serum cholinesterase activity associated with higher need for hemodynamic support. Patients with vascular disease are at increased risk for hemodynamic support as their basal levels of cholinesterase activities are lower than healthy non-vascular patients. Further research is needed on larger number of patients with the aim to understand the effect of severe atherosclerosis on decrease cholinesterase activity during anesthesia.

Declarations

Funding:

None

Conflict of interests:

None of the authors nor the individuals acknowledged below have any financial and personal relationships with other people or organizations that could inappropriately influence their work.

Author contributions

YBS, IM and SST participated in study conception and design. YBS, SB, ZE, EP, HE and SST performed the acquisition of data. SST, YBS, and IM participated in analysis and interpretation of data. YBS, SST, and IM drafted the manuscript and OR, DZ and IS helped in critical review of the manuscript. All of the authors have read and approved the submitted manuscript.

References

1. Lundeen G, Manohar M, Parks C. Systemic distribution of blood flow in swine while awake and during 1.0 and 1.5 MAC isoflurane anesthesia with or without 50% nitrous oxide. Anesth Analg. 1983;62(5):499–512.
2. Abbasivash R, Aghdashi MM, Sinaei B, Kheradmand F. The effects of propofol-midazolam-ketamine co-induction on hemodynamic changes and catecholamine response. J Clin Anesth.

2014;26(8):628–33.

3. Eisenhofer G. Sympathetic nerve function–assessment by radioisotope dilution analysis. Clin Auton Res. 2005;15(4):264–83.
4. Ebert TJ, Muzi M, Berens R, Goff D, Kampine JP. Sympathetic responses to induction of anesthesia in humans with propofol or etomidate. Anesthesiology. 1992;76(5):725–33.
5. g. BP. Autonomic Nervous System Anatomy and Physiology. In: Paul g. Barash Robert K. Stoelting, Michael K. Calahan, M. Christine Stock, Rafael Ortega Sam R. Sharar, Natatlie F. Holt BFC, editor. clinical Anesthesia. eighth edi. Philadelphia: Wolters Kluwer; 2017. p. 333.
6. Alcantara VM, Chautard-Freire-Maia EA, Scartezini M, Cerci MS, Braun-Prado K, Picheth G. Butyrylcholinesterase activity and risk factors for coronary artery disease. Scand J Clin Lab Invest. 2002;62(5):399–404.
7. Goliasch G, Haschemi A, Marculescu R, Endler G, Maurer G, Wagner O, et al. Butyrylcholinesterase activity predicts long-term survival in patients with coronary artery disease. Clin Chem. 2012;58(6):1055–8.
8. Ofek K, Soreq H. Cholinergic involvement and manipulation approaches in multiple system disorders. Chem Biol Interact. 2013;203(1):113–9.
9. Loewenstein-Lichtenstein Y, Schwarz M, Glick D, Norgaard-Pedersen B, Zakut H, Soreq H. Genetic predisposition to adverse consequences of anti-cholinesterases in “atypical” BCHE carriers. Nat Med. 1995;1(10):1082–5.
10. Davis L, Britten JJ, Morgan M. Cholinesterase. Its significance in anaesthetic practice. Anaesthesia. 1997;52(3):244–60.
11. Lahiri MK, Kannankeril PJ, Goldberger JJ. Assessment of autonomic function in cardiovascular disease: physiological basis and prognostic implications. J Am Coll Cardiol. 2008;51(18):1725–33.
12. Leeper NJ, Dewey FE, Ashley EA, Sandri M, Tan SY, Hadley D, et al. Prognostic value of heart rate increase at onset of exercise testing. Circulation. 2007;115(4):468–74.
13. Szymanski FM, Platek AE, Filipiak KJ. Is obstructive sleep apnea associated with the risk of ischemic stroke in patients with atrial fibrillation? Int J Cardiol. 2015;184:481–2.
14. Oda E. Associations between serum cholinesterase and incident hyper-LDL cholesterolemia, hypertriglyceridemia and hypo-HDL cholesterolemia as well as changes in lipid levels in a health screening population. Atherosclerosis. 2015;241(1):1–5.
15. CALLAWAY S, DAVIES DR, RUTLAND JP. Blood cholinesterase levels and range of personal variation in a healthy adult population. Br Med J. 1951;2(4735):812–6.
16. Assayag E Ben, Shenhar-Tsarfaty S, Ofek K, Soreq L, Bova I, Shopin L, et al. Serum cholinesterase activities distinguish between stroke patients and controls and predict 12-month mortality. Mol Med. 2010;
17. Bentz EW, Stoelting RK. Prolonged response to succinylcholine following pancuronium reversal with pyridostigmine. Anesthesiology. 1976;44(3):258–60.

18. Hakansson L. Mechanism of action of cholinesterase inhibitors in Alzheimer's disease. Acta Neurol Scand. 1993;149:7–9.
19. Stovner J, Oftedal N, Holmboe J. The inhibition of cholinesterases by pancuronium. Br J Anaesth. 1975;47(9):949–54.
20. Kao YJ, Tellez J, Turner DR. Dose-dependent effect of metoclopramide on cholinesterases and suxamethonium metabolism. Br J Anaesth. 1990;65(2):220–4.
21. Thomsen JL, Nielsen C V, Eskildsen KZ, Demant MN, Gatke MR. Awareness during emergence from anaesthesia: significance of neuromuscular monitoring in patients with butyrylcholinesterase deficiency. Br J Anaesth. 2015;115 Suppl:i78–88.
22. Muller A, Olbert M, Heymann A, Zahn PK, Plaschke K, von Dossow V, et al. Relevance of peripheral cholinesterase activity on postoperative delirium in adult surgical patients (CESARO): A prospective observational cohort study. Eur J Anaesthesiol. 2019;36(2):114–22.
23. Whittaker M. Plasma cholinesterase variants and the anaesthetist. Anaesthesia. 1980;35(2):174–97.
24. Fliser D, Laville M, Covic A, Fouque D, Vanholder R, Juillard L, et al. A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines on Acute Kidney Injury: Part 1: Definitions, conservative management and contrast-induced nephropathy. Nephrology Dialysis Transplantation. 2012.
25. Ellman GL, Courtney KD, Andres V, Featherstone RM. A new and rapid colorimetric determination of acetylcholinesterase activity. Biochem Pharmacol. 1961;
26. Shenhar-Tsarfaty S, Yayon N, Waiskopf N, Shapira I, Toker S, Zaltser D, et al. Fear and c-reactive protein cosynergize annual pulse increases in healthy adults. Proc Natl Acad Sci U S A. 2015;
27. Shenhar-Tsarfaty S, Brzezinski RY, Waiskopf N, Finkelstein A, Halkin A, Berliner S, et al. Blood acetylcholinesterase activity is associated with increased 10 year all-cause mortality following coronary angiography. Atherosclerosis. 2020;313.
28. Domenica Cappellini M, Motta I. Anemia in Clinical Practice-Definition and Classification: Does Hemoglobin Change With Aging? Seminars in Hematology. 2015.
29. Arbel Y, Shenhar-Tsarfaty S, Waiskopf N, Finkelstein A, Halkin A, Revivo M, et al. Decline in serum cholinesterase activities predicts 2-year major adverse cardiac events. Mol Med. 2014;20:38–45.
30. Goliasch G, Kleber ME, Richter B, Plischke M, Hoke M, Haschemi A, et al. Routinely available biomarkers improve prediction of long-term mortality in stable coronary artery disease: The Vienna and Ludwigshafen Coronary Artery Disease (VILCAD) risk score. Eur Heart J. 2012;
31. Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. British Journal of Anaesthesia. 2018.
32. Koenig J, Jarczok MN, Ellis RJ, Hillecke TK, Thayer JF. Heart rate variability and experimentally induced pain in healthy adults: A systematic review. European Journal of Pain (United Kingdom). 2014.

33. Baumert JH, Frey AW, Adt M. Analysis of heart rate variability. Background, methods, and possible use in anaesthesia. Anaesthesist. 1995;
34. Holtkamp C, Koos B, Unterberg M, Rahmel T, Bergmann L, Bazzi Z, et al. A novel understanding of postoperative complications: In vitro study of the impact of propofol on epigenetic modifications in cholinergic genes. PLoS One. 2019;
35. Hoke JF, Cunningham F, James MK, Muir KT, Hoffman WE. Comparative pharmacokinetics and pharmacodynamics of remifentanil, its principle metabolite (GR90291) and alfentanil in dogs. J Pharmacol Exp Ther. 1997;
36. Maranets I, Kain ZN. Preoperative anxiety and intraoperative anesthetic requirements. Anesth Analg. 1999;
37. Farbood A, Sahmeddini MA, Bayat S, Karami N. The effect of preoperative depression and anxiety on heart rate variability in women with breast cancer. Breast Cancer. 2020 Apr;

Figures

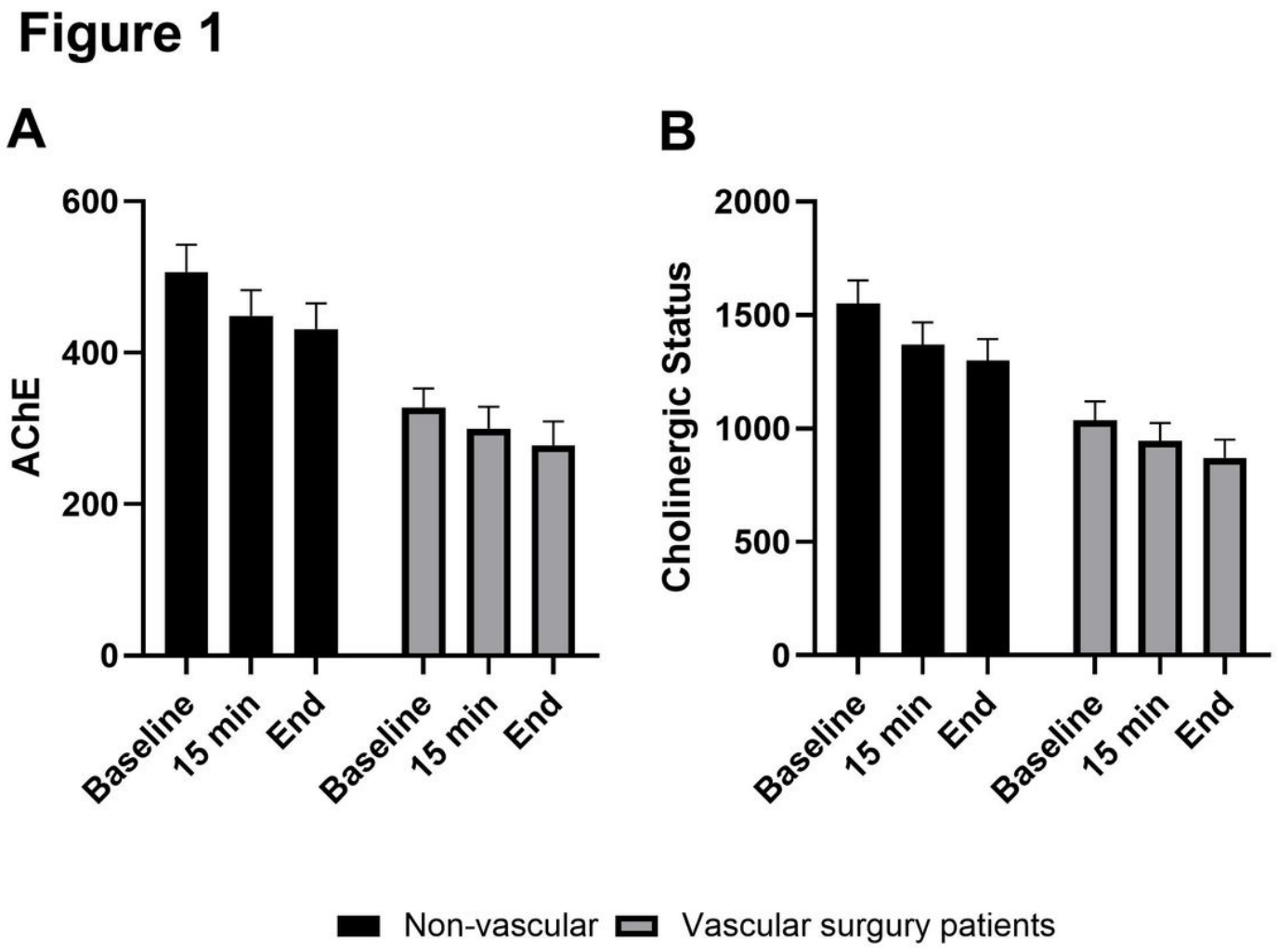

Figure 1

Mean AChE activity (a) and total cholinergic status (b) in vascular vs. non-vascular patients by time of measurement during anesthesia (baseline, 15 minutes and at the end of surgery)

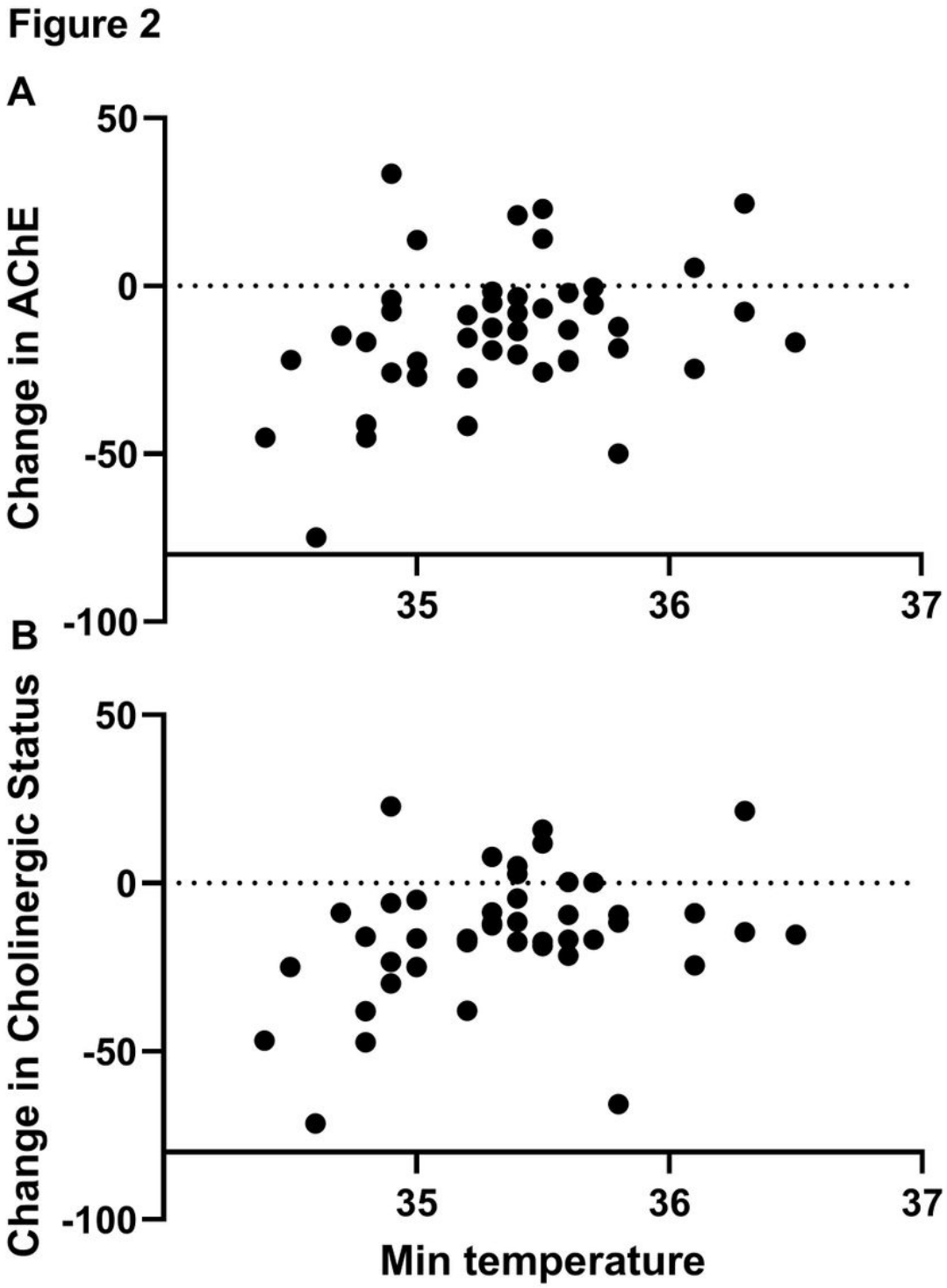

Figure 2

Correlation between minimal body temperature and the delta of AChE (a) and total cholinergic status (b) from the baseline to the end of anesthesia